Molina Clinical Policy
Laboratory Testing for the Diagnosis of Inflammatory Bowel Disease
Policy Number: G2121

POLICY SECTIONS

POLICY DESCRIPTION

Inflammatory bowel disease (IBD) is a class of inflammatory bowel disorders comprised of two major disorders: ulcerative colitis and Crohn's disease each with distinct pathologic and clinical characteristics (Peppercorn & Cheifetz, 2021).

Ulcerative colitis (UC) is a chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation limited to the mucosal layer of the colon (Silverberg et al., 2005) beginning at the rectum and may extend in a proximal and continuous fashion to involve other parts of the colon (Peppercorn & Kane, 2020).

Crohn's disease (CD) is characterized by patchy transmural inflammation (skip lesions) of the gastrointestinal tract resulting in sinus tracts, and ultimately microperforations and fistulae (Silverberg et al., 2005). It may also lead to fibrosis, strictures and to obstructive clinical presentations that are not typically seen in ulcerative colitis (Gasche et al., 2000; Peppercorn & Kane, 2019).

RELATED POLICIES

Policy No.	Policy Title
G2060	Fecal Analysis in The Diagnosis of Intestinal Dysbiosis
G2061	Fecal Calprotectin Testing
G2155	General Inflammation Testing
G2043	Celiac Disease Testing

INDICATIONS and/or LIMITATIONS OF COVERAGE

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

1. The use of serologic markers including, but not limited to, the following **DO NOT MEET COVERAGE CRITERIA** in the workup and monitoring of individuals with inflammatory bowel disease:
    a. anti-neutrophil cytoplasmic antibody (ANCA),
    b. anti-*Saccharomyces cerevisiae* antibody (ASCA),
    c. perinuclear anti-neutrophilic cytoplasmic antibody (pANCA),
    d. antibody to Escherichia coli outer membrane porin C (anti-OmpC),
    e. antibody to Pseudomonas fluorescens-associated sequence I2 (anti-I2),

f. anti-CBir1 flagellin antibody (anti-cBir1),

g. antichitobioside antibodies (ACCA IgA),

h. antilaminaribioside antibodies (ALCA IgG),

i. antimannobioside antibodies (AMCA IgG)

j. pyruvate kinase M2 (PKM2)

2. The use of diagnostic algorithm-based testing, including testing that combines serologic, genetic, and inflammation markers (such as Prometheus® testing) for the diagnosis or monitoring of individuals with inflammatory bowel disease, including Crohn's disease and ulcerative colitis, **DOES NOT MEET COVERAGE CRITERIA.**

3. Genetic testing for inflammatory bowel disease, including Crohn's disease and ulcerative colitis, **DOES NOT MEET COVERAGE CRITERIA.**

SCIENTIFIC BACKGROUND

The diagnoses of Crohn's disease (CD) and ulcerative colitis (UC) depend on a combination of clinical, laboratory, radiographic, endoscopic, and histological criteria. Differential diagnosis can be challenging but is highly important toward treatment and prognosis. Serological markers could be of value in differentiating CD from UC, in cases of indeterminate colitis, and in predicting the disease course of IBD (Peppercorn & Cheifetz, 2021; Peppercorn & Kane, 2018a, 2018b, 2019, 2020).

Investigations based on animal models have led to the current theory that chronic intestinal inflammation is the result of an aberrant immunologic response to commensal bacteria within the gut lumen (Blumberg, Saubermann, & Strober, 1999; Strober, Fuss, & Blumberg, 2002). Immune responses toward commensal enteric organisms have been investigated in CD and UC (Akasaka et al., 2015; D'Haens et al., 1998). Patients with IBD can have a loss of tolerance to specific bacterial antigens and autoantigens. These distinct antibody response patterns may indicate unique pathophysiological mechanisms in the progression of this complicated disease and may underlie the basis for the development of specific phenotypes (Landers et al., 2002; Peeters et al., 2001).

Numerous serological markers have been proposed as having utility in assessment of IBD patients. The most widely studied markers are the antineutrophil cytoplasmic antibodies (pANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA), particularly for diagnosing IBD and distinguishing CD from ulcerative colitis (Higuchi, 2020; Peppercorn & Kane, 2018a). pANCA is thought to be an antibody corresponding to histone 1 whereas ASCA is an antibody against mannan from baker's yeast (Mitsuyama et al., 2016). Although there have been promising results regarding the clinical validity of these antibodies (Reese et al., 2006; Ruemmele et al., 1998; Sandborn et al., 2000), its utility in indeterminate bowel disease is uncertain (Joossens et al., 2002; Peeters et al., 2001). ASCA were present in 50 percent of patients with celiac disease and described in cystic fibrosis and intestinal tuberculosis, suggesting that they may reflect a nonspecific immune response in small bowel disease (Condino et al., 2005; Granito et al., 2005).

Additional antibody tests under investigation include laminaribioside (ALCA), chitobioside (ACCA), CBir1 flagellin, OmpC, and I2. ALCA and ACCA are antiglycan antibodies whereas the CBir1 flagellin comes from an indigenous species of bacteria (Dotan et al., 2006; Targan et al., 2005). OmpC is an antibody to an outer membrane protein of *E. coli* and I2 is an antibody against the I2 component of *Pseudomonas fluorescens* (Mitsuyama et al., 2016). The accuracy and predictive value of antibody tests is uncertain (Wang, Shi, & Peng, 2017) and the prevalence of these antibodies in patients with a variety of inflammatory diseases affecting the gut has not been well-studied.

Additionally, bile acid deficiency--as indicated by serum 7α-hydroxy-4-cholesten-3-one (7C4)--has been documented in patients with IBS (Donato, Lueke, Kenyon, Meeusen, & Camilleri, 2018; Vijayvargiya et al., 2018). This test has shown utility as an alternative test to measuring bile acids in stool (Walters & Pattni, 2010), but it is not recommended in the workup for IBD.

Another proposed biomarker for IBD is serum pyruvate kinase M2 (PKM2), which is "emerging" in IBD as a mediator of inflammatory processes. Almousa, Morris, Fowler, Jones, and Alcorn (2018) evaluated its association with IBD and its correlation with traditional IBD indices, BD disease type, and intestinal microbiota. The authors found that serum PKM2 levels were 6 times higher in IBD patients compared to healthy controls. However, no sensitivity to disease phenotype or localization of inflammation was observed. A positive correlation between PKM2 and *Bacteroidetes* was identified, as well as a negative correlation between PKM2 and *Actinobacteria*. The investigators concluded that their data "suggests PKM2 as a putative biomarker for IBD and the dysbiosis of microflora in CD," but noted that further validation was required (Almousa et al., 2018).

Genetic studies have identified over 200 distinct susceptibility loci for irritable bowel disease with a significant portion of these overlapping with Crohn's and ulcerative colitis (Jostins et al., 2012; Liu et al., 2015). Most of these are located within introns, which more likely modulate the expression of proteins, with each only conferring a slight increase in risk (Snapper & Abraham, 2020). Altogether, the known loci only explain ~13% of variation in disease liability (Jostins et al., 2012). These results indicate that the genetic architecture of IBD represents that of multifactorial complex traits where a combination of multiple genes, along with the environment, lead to disease (Liu & Anderson, 2014). Given the low predictive value of individual genetic markers and high number of putative risk alleles, genetic testing does not currently offer much in terms of clinical utility (Lichtenstein et al., 2018; Liu & Anderson, 2014; McGovern, Kugathasan, & Cho, 2015; Shirts, von Roon, & Tebo, 2012).

Laboratory evidence of inflammation is common in IBD. Fecal calprotectin, lactoferrin, ESR and CRP have each been correlated with disease activity (Lewis, 2011; Menees, Powell, Kurlander, Goel, & Chey, 2015), but are not specific. Additional inflammatory markers including vascular endothelial growth factor, intercellular adhesion molecule, vascular adhesion molecule, and serum amyloid A offer no significant advantage (Shirts et al., 2012). Fecal calprotectin has been shown to be useful to help differentiate the presence of IBD from irritable bowel syndrome and in monitoring disease activity and response to treatment (Lichtenstein et al., 2018). Inflammation and calprotectin testing are discussed in greater detail in AHS-G2155 and AHS-G2061, respectively.

Clinical Validity and Utility

Panels to improve the predictive value of IBD testing incorporating serologic, genetic, and inflammation markers have been created (Plevy et al., 2013). The clinical validity and utility of antibody tests and panels of combinations of serologic tests for the diagnosis of IBD and the disease course and severity are still uncertain (Benor et al., 2010; Coukos et al., 2012; Kaul et al., 2012; Sura, Ahmed, Cheifetz, & Moss, 2014; Wang et al., 2017). For example, Prometheus Biosciences offers a series of tests intended for IBS. This series includes "IBDsgi Diagnostic", which evaluates 17 biomarkers (serological and genetic markers, intended to provide "diagnostic and prognostic clarity", "Crohn's Prognostic" (evaluates "proprietary serologic (anti-CBir1, anti-OMPC, DNAse sensitive pANCA) and genetic (NOD2 variants SNPs 8,12,13) markers"), and "Monitr" (evaluates 13 biomarkers to provide an "Endoscopic Healing Index Score" which represents endoscopic disease activity) (Prometheus, 2020).

Mitsuyama et al. (2014) conducted a multicenter study to explore the possible diagnostic utility of antibodies to the CD peptide (ACP) in patients with CD. A total of 196 patients with CD, 210 with UC, 98 with other intestinal conditions, and 183 healthy controls were examined. In CD patients, ACP had a higher sensitivity and specificity (63.3% and 91.0%, respectively) than ASCA (47.4% and 90.4%, respectively). ACP was also found to be negatively associated with disease duration. The authors concluded that "ACP, a newly proposed serologic marker, was significantly associated with CD and was highly diagnostic. Further investigation is needed across multiple populations of patients and ethnic groups, and more importantly, in prospective studies" (Mitsuyama et al., 2014).

Kaul et al. (2012) performed a meta-analysis/systemic review aimed to evaluate the diagnostic value, as well as the association of anti-glycan biomarkers with IBD susceptible gene variants, disease complications, and the need for surgery in IBD. A total of 23 studies were included consisting of 14 in the review and 9 in the meta-analysis. They found that "individually, anti-Saccharomyces cerevisiae antibodies (ASCA) had the highest diagnostic odds ratio (DOR) for differentiating IBD from healthy (DOR 21.1), and CD from UC (DOR 10.2…)" (Kaul et al., 2012). The authors concluded, "ASCA had the highest diagnostic value among individual anti-glycan markers. While anti-chitobioside carbohydrate antibody (ACCA) had the highest association with complications, ASCA and ACCA associated equally with the need for surgery" (Kaul et al., 2012).

Schoepfer, Trummler, Seeholzer, Seibold-Schmid, and Seibold (2008) aimed to determine the accuracy of fecal markers, C-reactive protein (CRP), blood leukocytes, and antibody panels for discriminating IBD from IBS. Sixty-four patients with IBD, 30 patients with IBS, and 42 healthy controls were included within the study. They found that "Overall accuracy of tests for discriminating IBD from IBS: IBD-SCAN 90%, PhiCal Test 89%, LEUKO-TEST 78%, Hexagon-OBTI 74%, CRP 73%, blood leukocytes 63%, CD antibodies (ASCA+/pANCA- or ASCA+/pANCA+) 55%, UC antibodies (pANCA+/ASCA-) 49%. ASCA and pANCA had an accuracy of 78% for detecting CD and 75% for detecting UC, respectively. The overall accuracy of IBD-SCAN and PhiCal Test combined with ASCA/pANCA for discriminating IBD from IBS was 92% and 91%, respectively (Schoepfer et al., 2008)."

Plevy et al. (2013) validated a diagnostic panel incorporating 17 markers. The markers were as follows: "8 serological markers (ASCA-IgA, ASCA-IgG, ANCA, pANCA, OmpC, CBir1, A4-Fla2, and FlaX), 4 genetic markers (ATG16L1, NKX2-3, ECM1, and STAT3), and 5 inflammatory markers (CRP, SAA, ICAM-1, VCAM-1, and VEGF)." A total of 572 patients with CD, 328 with UC, 427 non-IBD controls, and 183 controls were assessed. These results were compared to another panel with serological markers only. The extended panel increased the IBD vs non-IBD discrimination area under the curve from 0.80 to 0.87 and the CD vs UC from 0.78 to 0.93. The authors concluded that "incorporating a combination of serological, genetic, and inflammation markers into a diagnostic algorithm improved the accuracy of identifying IBD and differentiating CD from UC versus using serological markers alone" (Plevy et al., 2013).

Biasci et al. (2019) validated a 17-gene prognostic classifier. The classifier was intended to separate IBD patients into two subgroups of prognosis, IBDhi (poorer prognosis) and IBDlo. Two validation cohorts were used, one of CD (n=66) and one of UC (n=57). IBDhi (separated by the classifier) patients experienced both an "earlier need for treatment escalation (hazard ratio=2.65 (CD), 3.12 (UC)) and more escalations over time (for multiple escalations within 18 months: sensitivity=72.7% (CD), 100% (UC); negative predictive value=90.9% (CD), 100% (UC))" (Biasci et al., 2019).

Czub et al. (2014) compared PKM2 to fecal calprotectin (FC) as markers for mucosal inflammation in IBD. A total of 121 patients (75 with UC, 46 with CD) were compared to 35 healthy controls. The authors found that as a whole, PKM2 was "inferior" to FC. The differences in the area under curve were as follows: 0.10 (FC above PKM2, IBD), 0.14 (UC), and 0.03 (IBD). PKM2 was also considered inferior to FC in differentiating patients from mild UC from healthy patients by an AUC of 0.23 (Czub et al., 2014).

Kovacs et al. (2018) investigated "prognostic potential of classic and novel serologic antibodies regarding unfavorable disease course in a prospective ulcerative colitis (UC) patient cohort". The following auto-antibodies were measured: "anti-neutrophil cytoplasmic [ANCA], anti-DNA-bound-lactoferrin [anti-LFS], anti-goblet cell [anti-GAB] and anti-pancreatic [PAB: anti-CUZD1 and anti-GP2)])…anti-microbial (anti-Saccharomyces cerevisiae [ASCA] IgG/IgA and anti-OMP Plus™ IgA) antibodies". A total of 187 patients were included. The authors found a total of "73.6%, 62.4% and 11.2% of UC patients were positive for IgA/IgG type of atypical perinuclear-ANCA, anti-LFS and anti-GAB, respectively". Occurrences of PABs were 9.6%, ASCA IgA/IgG was 17.6%, and anti-OMP IgA was 19.8%. "IgA type PABs" were found to be more prevalent in patients with primary sclerosing cholangitis ("37.5% vs. 4.7% for anti-CUZD1 and 12.5% vs. 0% for anti-GP2"). IgA type ASCA was associated with a higher risk for requiring long-term immunosuppressant therapy. The authors found that none of the autoantibodies, either alone or in combination, were associated with the "risk of development of extensive disease or colectomy", although "multiple antibody positivity [≥3]" was associated with UC-related hospitalization. Overall, the authors concluded that "Even with low prevalence rates, present study gives further evidence to the role of certain antibodies as markers for distinct phenotype and disease outcome in UC. Considering the result of the multivariate analysis the novel antibodies investigated do not seem to be associated with poor clinical outcome in UC, only a classic antibody, IgA subtype ASCA remained an independent predictor of long-term immunosuppressive therapy." (Kovacs et al., 2018)

Ben-Shachar et al. (2019) evaluated the impact of genotype variations on serological biomarkers. The authors examined three *NOD2* variants (1007fs, G908R, R702W) and an *ATG16L1* variant (A300T). Then, the authors analyzed the antiglycan antibodies anti-*Saccharomyces cerevisiae* (ASCA), antilaminaribioside (ALCA), antichitobioside (ACCA), and antimannobioside carbohydrate (AMCA). A total of 308 IBD patients were included, "130 with Crohn's Disease (CD), 67 with ulcerative colitis (UC), 111 with UC and an ileal pouch (UC-pouch), and 74 healthy controls". ACCA was found to be "positive" in 28% of CD patients with the *ATG16L1* A300T variant, compared to only 3% in patients without the variant. ASCA was found to be positive in 86% of patients with the 1007fs variant, compared to 36% without the variant. UC-pouch patients with the 1007fs variant were also found to have "elevated" ASCA and

ALCA levels compared to those without (50% vs 7% and 50% vs 8% respectively). The authors also found that the genetic variants were not associated with serologic responses in healthy controls and "unoperated" UC patients. The authors concluded that "Genetic variants may have disease-specific phenotypic (serotypic) effects. This implies that genetic risk factors may also be disease modifiers." (Ben-Shachar et al., 2019)

Ahmed et al. (2019) examined the association between six serological markers and Crohn's Disease (CD) activity. The six markers evaluated were "ASCA-IgA, ASCA-IgG, anti-OmpC IgA, anti-CBir1 IgG, anti-A4Fla2 IgG and anti-FlaX IgG". A total of 135 patients were included. The authors found that CD patients with high anti-CBir1 IgG at baseline were 2.06 times more likely to have active clinical disease. The other five autoantibodies were not found to have significant impact on clinical course. The authors concluded that "High levels of anti-CBir1 IgG appear to be associated with a greater likelihood of active CD. Whether routine baseline testing for anti-CBir1 IgG to predict a more active clinical course is warranted needs more research." (Ahmed, Lysek, Zhang, & Malik, 2020; Duarte-Silva et al., 2019)

Eltabbakh (2021) studied the diagnostic utility of beta 2-microglobulin (B2-M) as a biomarker in patients with IBS and UC. B2-M is a protein released by activated T and B lymphocytes and has shown to increase in inflammatory conditions. 40 patients with UC, 20 patients with IBS, and 20 healthy subjects were enrolled in the study. Overall, there was a higher mean of B2-M values in the UC patients (1.93) than IBS patients (1.51) or healthy subjects (1.43). At a cut off value of >1.5, sensitivity (75%), specificity (70%), PPV (83.3%), NPV (58.3%), and accuracy (0.753%) were measured. It was concluded that "B2-M level may have a diagnostic and differentiating utility between UC cases and IBS-D type as well as a potential indicator of disease activation in UC patients" (Eltabbakh, 2021).

Gao & Zhang (2021) studied the use of serological markers for the diagnosis of Crohn's disease. 196 suspected CD patients were enrolled in the study and ELISA was used to study the expression of various biomarkers including ASCA-IgG, ASCA-IgA, AYMA-IgG, AYCA-IgA, FI2Y-IgG, and pANCA. Overall, ASCA was found to be the most accurate serological marker for the differential diagnosis of CD. It was also noted that a combination of markers resulted in a higher sensitivity and NPV. There was no relation noted between the expression of ASCA and disease behavior at diagnosis (Gao & Zhang, 2021).

GUIDELINES AND RECOMMENDATIONS

American Gastroenterological Association (AGA, 2015)

No guideline or position statement from AGA on the use of immunologic or genetic markers for the diagnosis of inflammatory bowel disease was found. The AGA assessment algorithms used for both Crohn's disease and ulcerative colitis do not include genetic testing or combinatorial serologic-genetic testing approaches, such as the Prometheus® testing methodology (AGA, 2015).

American College of Gastroenterology (ACG) (Lacy et al., 2021; Lichtenstein et al., 2018; Rubin, Ananthakrishnan, Siegel, Sauer, & Long, 2019)

The ACG published guidelines (Lichtenstein et al., 2018) on the management of Crohn's disease which state:

- "The diagnosis of Crohn's disease (CD) is based on a combination of clinical presentation and endoscopic, radiologic, histologic, and pathologic findings that demonstrate some degree of focal, asymmetric, and transmural granulomatous inflammation of the luminal GI tract. Laboratory testing is complementary in assessing disease severity and complications of disease. There is no single laboratory test that can make an unequivocal diagnosis of CD. The sequence of testing is dependent on presenting clinical features."
- "Initial laboratory investigation should include evaluation for inflammation, anemia, dehydration, and malnutrition."
- "Genetic testing is not indicated to establish the diagnosis of Crohn's disease."
- "Routine use of serologic markers of IBD to establish the diagnosis of Crohn's disease is not indicated."

- The ACG guidelines on Ulcerative Colitis in adults (Rubin et al., 2019) state:

- "We recommend against serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence)."

- "We recommend against serologic antibody testing to determine the prognosis of UC (strong recommendation, very low quality of evidence)."

- The ACG also mentions perinuclear antineutrophil cytoplasmic antibodies (pANCAs) as a proposed serological marker, but they observe that "there is currently no role for such testing to determine the likelihood of disease evolution and prognosis" and that the marker has low sensitivity for diagnostic purposes.

- Overall, "the yield of genetic or serologic markers in predicting severity and course of UC has been modest at best, and their use cannot be recommended in routine clinical practice based on available data (Rubin et al., 2019)."

The ACG released guidelines on management of IBS in adults. The recommendations state:

- "We recommend that serologic testing be performed to rule out celiac disease (CD) in patients with IBS and diarrhea symptoms.

- We suggest that either fecal calprotectin or fecal lactoferrin and C-reactive protein be checked in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease.

- We recommend against routine stool testing for enteric pathogens in all patients with IBS" (Lacy et al., 2021).

European Crohn's and Colitis Organisation (ECCO) (Gomollón et al., 2016; F. Magro et al., 2020; Fernando Magro et al., 2017)

ECCO states that the Montréal classification of CD is advocated. Therefore, "genetic tests or serological markers should currently not be used to classify CD in clinical practice" (Gomollón et al., 2016).

In a 2017 update for UC, ECCO states that "the routine clinical use of genetic or serological molecular markers is not recommended for the classification of ulcerative colitis." ECCO also notes that the most widely studied marker is the pANCAs, but they have "limited sensitivity" and "their routine use for the diagnosis of UC and for therapeutic decisions is not clinically justified" (Fernando Magro et al., 2017).

ECCO also published a "harmonization of the approach to Ulcerative Colitis Histopathology". A section titled "Correlation of Histological Scores with Biomarkers" is included. However, only fecal biomarkers (such as fecal lactoferrin and calprotectin) are mentioned, with no mention of serological biomarkers (F. Magro et al., 2020).

World Gastroenterology Organisation (WGO) (Bernstein et al., 2016)

Concerning the use of p-ANCA and ASCA to diagnose UC and CD, the WGO states, "These tests are unnecessary as screening tests, particularly if endoscopy or imaging is going to be pursued for more definitive diagnoses. p-ANCA may be positive in Crohn's colitis and hence may not be capable of distinguishing CD from UC in otherwise unclassified colitis. ASCA is more specific for CD. These tests may have added value when there may be subtly abnormal findings, but a definitive diagnosis of inflammatory bowel disease is lacking. They may also be helpful if considering more advanced endoscopic techniques such as capsule endoscopy or double-balloon endoscopy, such that a positive ASCA test may provide stronger reasons for evaluating the small bowel." Later, the WGO also notes, "There are several other antibody tests, mostly for microbial antigens, that increase the likelihood of CD either singly, in combination, or as a sum score of the ELISA results for a cluster of antibodies. These tests are costly and not widely available. The presence of these antibodies, including a positive ASCA, would increase the likelihood that an unclassified IBD-like case represents Crohn's disease (Bernstein et al., 2016)."

Working Group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America (Bousvaros et al., 2007)

A clinical report (Bousvaros et al., 2007) noted that:

> "A positive ANCA does not differentiate between UC and Crohn colitis."
>
> "Genetic testing cannot as yet reliably differentiate UC from CD of the colon."

The Working Group also observed that in the largest study of prospective markers for UC, the majority of patients remained seronegative for both ASCA and ANCA.

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) (Kelsen et al., 2019)

NASPGHAN published a guideline regarding the management of patients with "Very Early-Onset Inflammatory Bowel Disease (VEO-IBD)". This guideline defines this cohort as a patient of the pediatric IBD population presenting at under 6 years of age. The guideline makes the following remarks on evaluation of IBD in this population:

- "…genetic sequencing is often necessary to identify the specific monogenic forms of VEO-IBD, or to confirm a suspected defect."
- "Targeted panels should be performed first in cases of infantile onset IBD, when the phenotype is consistent with a known defect, history of consanguinity, and abnormal immunology studies."
- "Currently, WES is most often performed in the setting of a negative targeted panel, however, there are select cases in which WES may be indicated instead of a targeted panel, such as those patients who present with a phenotype that is not previously described."
- "At this time, WGS should be reserved for cases in which WES is negative, yet there remains a high suspicion of a monogenic defect given the young age of onset, disease severity, family history, and complex phenotype including associated autoimmunity."
- "In general, the gene defects that have been detected with the highest frequency in patients with VEO-IBD can prompt specific targeted therapies that include: defects that lead to CGD (NADPH complex defects), IL-10R and XIAP." (Kelsen et al., 2019)

National Institute for Health and Care Excellence (NICE, 2019a, 2019b)

NICE does not mention any serological or genetic biomarkers in its reviews of management of UC or CD (NICE, 2019a, 2019b).

British Society of Gastroenterology (BSG) (Lamb et al., 2019; Vasant et al., 2021)

The BSG published guidelines on the "management of inflammatory bowel disease [IBD] in adults". In it, they made the following comments regarding use of biomarkers in IBD:

- "…more evidence is also needed of the role of faecal calprotectin or other biomarkers as non-invasive surrogates for mucosal healing."
- "Further studies are required to evaluate the use of drug levels and biomarkers to determine personalized dosing for patients."
- "If a response [to treatment] is unclear, then measurement of biomarkers, serum C-reactive protein and faecal calprotectin, or comparison of disease activity scores or PROMs with baseline values, may be helpful."
- "We suggest that genetic testing for monogenic disorders should be considered in adolescents and young adults who have had early onset (before 5 years of age) or particularly aggressive, refractory or unusual IBD presentations (GRADE: weak recommendation, very low-quality evidence." (Lamb et al., 2019)

In 2021, the BSG released guidelines on management of irritable bowel syndrome. The BSG suggests that "all patients presenting with symptoms of IBS for the first time in primary care should have a full blood count, C reactive protein or erythrocyte sedimentation rate, coeliac serology and, in patients <45 years of age with diarrhea, a faecal calprotectin to exclude inflammatory bowel disease. Local and national guidelines for colorectal and ovarian cancer screening should be followed, where indicated" (Vasant et al., 2021).

European Crohn's and Colitis Organisation (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) (Maaser et al., 2018)

- These joint guidelines include some relevant items on inflammatory bowel disease (IBD), which includes both Crohn's disease (CD) and ulcerative colitis (UC). These items include:
- "A single reference standard for the diagnosis of Crohn's disease [CD] or ulcerative colitis [UC] does not exist. The diagnosis of CD or UC is based on a combination of clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations."
- "Genetic or serological testing is currently not recommended for routine diagnosis of CD or UC."
- "On diagnosis, complementary investigations should focus on markers of disease activity, malnutrition, or malabsorption."
- "Serological markers may be used to support a diagnosis, though the accuracy of the best available tests [pANCA and ASCAs] is rather limited and hence ineffective at differentiating colonic CD from UC. Similarly, the additional diagnostic value of antiglycan and antimicrobial antibodies, such as anti-OmpC and CBir1, is small." (Maaser et al., 2018)

European Crohn's and Colitis Organisation (ECCO) and European Society of Pediatric Gastroenterology, Hepatology and Nutrition (European Society for Paediatric Gastroenterology Hepatology and Nutrition) (Maaser et al., 2018; Turner et al., 2018)

This joint guideline was published regarding "Management of Paediatric Ulcerative Colitis" Although there was no mention of serological markers, the guideline did make this comment on "very early-onset inflammatory bowel disease presenting as colitis", which is as follows:

- "Unusual disease evolution, history of recurrent infections, HLH [hemophagocytic lymphocytic histiocytosis], and non-response to multiple IBD medications may indicate an underlying genetic defect which should prompt genetic and/or immunological analyses at any age during childhood." (Turner et al., 2018)

World Society of Emergency Surgery and the American Association for the Surgery of Trauma (De Simone et al., 2021)

WSES and AAST released joint guidelines on the management of inflammatory bowel disease in the emergency setting. When assessing an acute abdomen in patients with IBD, "laboratory tests including full blood count, electrolytes, liver enzymes, inflammatory biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and serum albumin and pre-albumin (to assess nutritional status and degree of inflammation) are mandatory" (De Simone et al., 2021).

APPLICABLE STATE AND FEDERAL REGULATIONS

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member (e.g., Local Coverage Determinations [LCDs]) or National Coverage Determinations [NCDs] for Medicare and/or state coverage for Medicaid), then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

A search for "Crohn," "colitis," and "irritable bowel" on July 25, 2021, yielded zero results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

APPLICABLE CPT / HCPCS PROCEDURE CODES

CPT	Code Description
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81479	Unlisted molecular pathology procedure
82397	Chemiluminescent assay
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
86021	Antibody identification; leukocyte antibodies
86036	Antineutrophil cytoplasmic antibody (ANCA); screen, each antibody
86037	Antineutrophil cytoplasmic antibody (ANCA); titer, each antibody
86255	Fluorescent noninfectious agent antibody; screen, each antibody
86671	Antibody; fungus, not elsewhere specified
88346	Immunofluorescence, per specimen; initial single antibody stain procedure
88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
0164U	Gastroenterology (irritable bowel syndrome [IBS]), immunoassay for anti-CdtB and anti-vinculin antibodies, utilizing plasma, algorithm for elevated or not elevated qualitative results Proprietary test: ibs-smart™ Lab/Manufacturer: Gemelli Biotech
0176U	Cytolethal distending toxin B (CdtB) and vinculin IgG antibodies by immunoassay (ie, ELISA) Proprietary test: IBSchek® Lab/Manufacturer: Commonwealth Diagnostics International, Inc
0203U	Autoimmune (inflammatory bowel disease), mRNA, gene expression profiling by quantitative RT-PCR, 17 genes (15 target and 2 reference genes), whole blood, reported as a continuous risk score and classification of inflammatory bowel disease aggressiveness Proprietary test: PredictSURE IBD™ Test Lab/Manufacturer: KSL Diagnostics

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

Approval History

Type	Date	Action
Effective Date	7/1/2022	New Policy
Revision Date		

EVIDENCE-BASED SCIENTIFIC REFERENCES

AGA. Identification, Assessment and Initial Medical Treatment in Crohn's Disease CLINICAL DECISION SUPPORT TOOL. Retrieved from https://s3.amazonaws.com/agaassets/pdf/guidelines/IBDCarePathway.pdf

AGA. (2015). Ulcerative Colitis CLINICAL CARE PATHWAY. Retrieved from https://s3.amazonaws.com/agaassets/pdf/guidelines/UlcerativeColitis/index.html

Ahmed, Z., Lysek, M., Zhang, N., & Malik, T. A. (2020). Association Between Serological Markers and Crohn's Disease Activity. *J Clin Med Res, 12*(1), 6-12. doi:10.14740/jocmr4016

Akasaka, E., Nakano, H., Korekawa, A., Fukui, T., Kaneko, T., Koga, H., . . . Sawamura, D. (2015). Anti-laminin gamma1 pemphigoid associated with ulcerative colitis and psoriasis vulgaris showing autoantibodies to laminin gamma1, type XVII collagen and laminin-332. *Eur J Dermatol, 25*(2), 198-199. doi:10.1684/ejd.2014.2499

Almousa, A. A., Morris, M., Fowler, S., Jones, J., & Alcorn, J. (2018). Elevation of serum pyruvate kinase M2 (PKM2) in IBD and its relationship to IBD indices. *Clin Biochem, 53*, 19-24. doi:https://doi.org/10.1016/j.clinbiochem.2017.12.007

Ben-Shachar, S., Finezilber, Y., Elad, H., Rabinowitz, K., Goren, I., Isakov, O., . . . Dotan, I. (2019). Genotype-Serotype Interactions Shed Light on Genetic Components of Inflammatory Bowel Diseases. *Inflamm Bowel Dis, 25*(2), 336-344. doi:10.1093/ibd/izy231

Benor, S., Russell, G. H., Silver, M., Israel, E. J., Yuan, Q., & Winter, H. S. (2010). Shortcomings of the inflammatory bowel disease Serology 7 panel. *Pediatrics, 125*(6), 1230-1236. doi:10.1542/peds.2009-1936

Bernstein, C. N., Eliakim, A., Fedail, S., Fried, M., Gearry, R., Goh, K. L., . . . LeMair, A. (2016). World Gastroenterology Organisation Global Guidelines Inflammatory Bowel Disease: Update August 2015. *J Clin Gastroenterol, 50*(10), 803-818. doi:10.1097/mcg.0000000000000660

Biasci, D., Lee, J. C., Noor, N. M., Pombal, D. R., Hou, M., Lewis, N., . . . Smith, K. G. C. (2019). A blood-based prognostic biomarker in IBD. *Gut, 68*(8), 1386. doi:10.1136/gutjnl-2019-318343

Blumberg, R. S., Saubermann, L. J., & Strober, W. (1999). Animal models of mucosal inflammation and their relation to human inflammatory bowel disease. *Curr Opin Immunol, 11*(6), 648-656. Retrieved from https://www.sciencedirect.com/science/article/pii/S0952791599000321

Bousvaros, A., Antonioli, D. A., Colletti, R. B., Dubinsky, M. C., Glickman, J. N., Gold, B. D., . . . Russo, P. A. (2007). Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. *J Pediatr Gastroenterol Nutr, 44*(5), 653-674. doi:10.1097/MPG.0b013e31805563f3

Condino, A. A., Hoffenberg, E. J., Accurso, F., Penvari, C., Anthony, M., Gralla, J., & O'Connor, J. A. (2005). Frequency of ASCA seropositivity in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr, 41*(1), 23-26. Retrieved from http://dx.doi.org/

Coukos, J. A., Howard, L. A., Weinberg, J. M., Becker, J. M., Stucchi, A. F., & Farraye, F. A. (2012). ASCA IgG and CBir antibodies are associated with the development of Crohn's disease and fistulae following ileal pouch-anal anastomosis. *Dig Dis Sci, 57*(6), 1544-1553. doi:10.1007/s10620-012-2050-6

Czub, E., Nowak, J. K., Szaflarska-Poplawska, A., Grzybowska-Chlebowczyk, U., Landowski, P., Moczko, J., . . . Walkowiak, J. (2014). Comparison of fecal pyruvate kinase isoform M2 and calprotectin in assessment of pediatric inflammatory bowel disease severity and activity. *Acta Biochim Pol, 61*(1), 99-102.

D'Haens, G. R., Geboes, K., Peeters, M., Baert, F., Penninckx, F., & Rutgeerts, P. (1998). Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology, 114*(2), 262-267. Retrieved from http://dx.doi.org/

De Simone, B., Davies, J., Chouillard, E., Di Saverio, S., Hoentjen, F., Tarasconi, A., . . . Catena, F. (2021). WSES-AAST guidelines: management of inflammatory bowel disease in the emergency setting. *World Journal of Emergency Surgery, 16*(1), 23. doi:10.1186/s13017-021-00362-3

Donato, L. J., Lueke, A., Kenyon, S. M., Meeusen, J. W., & Camilleri, M. (2018). Description of analytical method and clinical utility of measuring serum 7-alpha-hydroxy-4-cholesten-3-one (7aC4) by mass spectrometry. *Clin Biochem, 52*, 106-111. doi:10.1016/j.clinbiochem.2017.10.008

Dotan, I., Fishman, S., Dgani, Y., Schwartz, M., Karban, A., Lerner, A., . . . Halpern, Z. (2006). Antibodies against laminaribioside and chitobioside are novel serologic markers in Crohn's disease. *Gastroenterology, 131*(2), 366-378. doi:10.1053/j.gastro.2006.04.030

Duarte-Silva, M., Afonso, P. C., de Souza, P. R., Peghini, B. C., Rodrigues-Júnior, V., & de Barros Cardoso, C. R. (2019). Reappraisal of antibodies against Saccharomyces cerevisiae (ASCA) as persistent biomarkers in quiescent Crohn's disease. *Autoimmunity, 52*(1), 37-47. doi:10.1080/08916934.2019.1588889

Eltabbakh, M. (2021). Diagnostic Utility of Beta 2 Microglobulin in Patients with Irritable Bowel Syndrome and Ulcerative Colitis. *Egyptian Journal of Medical Microbiology 30*. doi:https://doi.org/10.51429/EJMM30213

Gao, X., & Zhang, Y. (2021). Serological markers facilitate the diagnosis of Crohn's disease. *Postgraduate Medicine, 133*(3), 286-290. doi:10.1080/00325481.2021.1873649

Gasche, C., Scholmerich, J., Brynskov, J., D'Haens, G., Hanauer, S. B., Irvine, E. J., . . . Sutherland, L. R. (2000). A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis, 6*(1), 8-15. Retrieved from http://dx.doi.org/

Gomollón, F., Dignass, A., Annese, V., Tilg, H., Van Assche, G., Lindsay, J. O., . . . on behalf of, E. (2016). 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *Journal of Crohn's and Colitis, 11*(1), 3-25. doi:10.1093/ecco-jcc/jjw168

Granito, A., Zauli, D., Muratori, P., Muratori, L., Grassi, A., Bortolotti, R., . . . Volta, U. (2005). Anti-Saccharomyces cerevisiae and perinuclear anti-neutrophil cytoplasmic antibodies in coeliac disease before and after gluten-free diet. *Aliment Pharmacol Ther, 21*(7), 881-887. doi:10.1111/j.1365-2036.2005.02417.x

Higuchi, L. M., Bousvaros, Athos. (2020). Clinical presentation and diagnosis of inflammatory bowel disease in children. Retrieved from https://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-inflammatory-bowel-disease-in-children?search=and%20anti-Saccharomyces%20cerevisiae%20antibodies&source=search_result&selectedTitle=1~11&usage_type=default&display_rank=1#H1679701079

Joossens, S., Reinisch, W., Vermeire, S., Sendid, B., Poulain, D., Peeters, M., . . . Colombel, J. F. (2002). The value of serologic markers in indeterminate colitis: a prospective follow-up study. *Gastroenterology, 122*(5), 1242-1247. Retrieved from http://dx.doi.org/

Jostins, L., Ripke, S., Weersma, R. K., Duerr, R. H., McGovern, D. P., Hui, K. Y., . . . Cho, J. H. (2012). Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature, 491*(7422), 119-124. doi:10.1038/nature11582

Kaul, A., Hutfless, S., Liu, L., Bayless, T. M., Marohn, M. R., & Li, X. (2012). Serum anti-glycan antibody biomarkers for inflammatory bowel disease diagnosis and progression: a systematic review and meta-analysis. *Inflamm Bowel Dis, 18*(10), 1872-1884. doi:10.1002/ibd.22862

Kelsen, J. R., Sullivan, K. E., Rabizadeh, S., Singh, N., Snapper, S., Elkadri, A., & Grossman, A. B. (2019). NASPGHAN Position Paper on The Evaluation and Management for Patients with Very Early-Onset Inflammatory Bowel Disease (VEO-IBD). *J Pediatr Gastroenterol Nutr*. doi:10.1097/mpg.0000000000002567

Kovacs, G., Sipeki, N., Suga, B., Tornai, T., Fechner, K., Norman, G. L., . . . Papp, M. (2018). Significance of serological markers in the disease course of ulcerative colitis in a prospective clinical cohort of patients. *PLoS One, 13*(3), e0194166. doi:10.1371/journal.pone.0194166

Lacy, B. E., Pimentel, M., Brenner, D. M., Chey, W. D., Keefer, L. A., Long, M. D., & Moshiree, B. (2021). ACG Clinical Guideline: Management of Irritable Bowel Syndrome. *Official journal of the American College of Gastroenterology | ACG, 116*(1), 17-44. doi:10.14309/ajg.0000000000001036

Lamb, C. A., Kennedy, N. A., Raine, T., Hendy, P. A., Smith, P. J., Limdi, J. K., . . . Hawthorne, A. B. (2019). British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut, 68*(Suppl 3), s1. doi:10.1136/gutjnl-2019-318484

Landers, C. J., Cohavy, O., Misra, R., Yang, H., Lin, Y. C., Braun, J., & Targan, S. R. (2002). Selected loss of tolerance evidenced by Crohn's disease-associated immune responses to auto- and microbial antigens. *Gastroenterology, 123*(3), 689-699. Retrieved from https://www.sciencedirect.com/science/article/abs/pii/S0016508502001592

Lewis, J. D. (2011). The Utility of Biomarkers in the Diagnosis and Therapy of Inflammatory Bowel Disease. *Gastroenterology, 140*(6), 1817-1826 e1812. doi:10.1053/j.gastro.2010.11.058

Lichtenstein, G. R., Loftus, E. V., Isaacs, K. L., Regueiro, M. D., Gerson, L. B., & Sands, B. E. (2018). ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol, 113*(4), 481-517. doi:10.1038/ajg.2018.27

Liu, J. Z., & Anderson, C. A. (2014). Genetic studies of Crohn's disease: Past, present and future. In *Best Pract Res Clin Gastroenterol* (Vol. 28, pp. 373-386).

Liu, J. Z., van Sommeren, S., Huang, H., Ng, S. C., Alberts, R., Takahashi, A., . . . Weersma, R. K. (2015). Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet, 47*(9), 979-986. doi:10.1038/ng.3359

Maaser, C., Sturm, A., Vavricka, S. R., Kucharzik, T., Fiorino, G., Annese, V., . . . Stoker, J. (2018). ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *Journal of Crohn's and Colitis, 13*(2), 144-164K. doi:10.1093/ecco-jcc/jjy113

Magro, F., Doherty, G., Peyrin-Biroulet, L., Svrcek, M., Borralho, P., Walsh, A., . . . Feakins, R. (2020). ECCO Position Paper: Harmonisation of the approach to Ulcerative Colitis Histopathology. *J Crohns Colitis*. doi:10.1093/ecco-jcc/jjaa110

Magro, F., Gionchetti, P., Eliakim, R., Ardizzone, S., Armuzzi, A., Barreiro-de Acosta, M., . . . Colitis, O. (2017). Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *Journal of Crohn's and Colitis, 11*(6), 649-670. doi:10.1093/ecco-jcc/jjx008

McGovern, D., Kugathasan, S., & Cho, J. H. (2015). Genetics of Inflammatory Bowel Diseases. *Gastroenterology, 149*(5), 1163-1176 e1162. doi:10.1053/j.gastro.2015.08.001

Menees, S. B., Powell, C., Kurlander, J., Goel, A., & Chey, W. D. (2015). A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol, 110*(3), 444-454. doi:10.1038/ajg.2015.6

Mitsuyama, K., Niwa, M., Masuda, J., Yamasaki, H., Kuwaki, K., Takedatsu, H., . . . Sata, M. (2014). Possible diagnostic role of antibodies to Crohn's disease peptide (ACP): results of a multicenter study in a Japanese cohort. *J Gastroenterol, 49*(4), 683-691. doi:10.1007/s00535-013-0916-9

Mitsuyama, K., Niwa, M., Takedatsu, H., Yamasaki, H., Kuwaki, K., Yoshioka, S., . . . Torimura, T. (2016). Antibody markers in the diagnosis of inflammatory bowel disease. *World J Gastroenterol, 22*(3), 1304-1310. doi:10.3748/wjg.v22.i3.1304

NICE. (2019a). Crohn's disease overview. Retrieved from https://pathways.nice.org.uk/pathways/crohns-disease#content=view-index

NICE. (2019b). Ulcerative colitis overview. Retrieved from https://pathways.nice.org.uk/pathways/ulcerative-colitis#content=view-node%3Anodes-diagnostic-and-prognostic-tests

Peeters, M., Joossens, S., Vermeire, S., Vlietinck, R., Bossuyt, X., & Rutgeerts, P. (2001). Diagnostic value of anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease. *Am J Gastroenterol, 96*(3), 730-734. doi:10.1111/j.1572-0241.2001.03613.x

Peppercorn, M., & Cheifetz, A. S. (2021). Definition, epidemiology, and risk factors in inflammatory bowel disease - UpToDate. In K. Robson (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/definition-epidemiology-and-risk-factors-in-inflammatory-bowel-disease?source=see_link

Peppercorn, M., & Kane, S. (2018a). Clinical manifestations, diagnosis and prognosis of Crohn disease in adults - UpToDate. In K. Robson (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-crohn-disease-in-adults?source=search_result&search=antibodies%20inflammatory%20bowel%20disease&selectedTitle=2~150#H12689155

Peppercorn, M., & Kane, S. (2018b). Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults - UpToDate. In K. Robson (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-ulcerative-colitis-in-adults?source=search_result&search=inflammatory%20bowel%20disease&selectedTitle=1~150

Peppercorn, M., & Kane, S. (2019). Clinical manifestations, diagnosis and prognosis of Crohn disease in adults - UpToDate. In K. Robson (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-crohn-disease-in-adults?source=search_result&search=antibodies%20inflammatory%20bowel%20disease&selectedTitle=2~150#H12689155

Peppercorn, M., & Kane, S. (2020). Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults - UpToDate. In K. Robson (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-ulcerative-colitis-in-adults?source=search_result&search=inflammatory%20bowel%20disease&selectedTitle=1~150

Plevy, S., Silverberg, M. S., Lockton, S., Stockfisch, T., Croner, L., Stachelski, J., . . . Singh, S. (2013). Combined serological, genetic, and inflammatory markers differentiate non-IBD, Crohn's disease, and ulcerative colitis patients. *Inflamm Bowel Dis, 19*(6), 1139-1148. doi:10.1097/MIB.0b013e318280b19e

Prometheus. (2020). Revolutionizing GI Diagnostics with Precision. Retrieved from https://www.prometheusbiosciences.com/ibd-sgi/

Reese, G. E., Constantinides, V. A., Simillis, C., Darzi, A. W., Orchard, T. R., Fazio, V. W., & Tekkis, P. P. (2006). Diagnostic precision of anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. *Am J Gastroenterol, 101*(10), 2410-2422. doi:10.1111/j.1572-0241.2006.00840.x

Rubin, D. T., Ananthakrishnan, A. N., Siegel, C. A., Sauer, B. G., & Long, M. D. (2019). ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol, 114*(3), 384-413. doi:10.14309/ajg.0000000000000152

Ruemmele, F. M., Targan, S. R., Levy, G., Dubinsky, M., Braun, J., & Seidman, E. G. (1998). Diagnostic accuracy of serological assays in pediatric inflammatory bowel disease. *Gastroenterology, 115*(4), 822-829. Retrieved from http://dx.doi.org/

Sandborn, W. J., Loftus, E. V., Colombel, J. F., Fleming, K., Seibold, F., Homburger, H. A., . . . Targan, S. R. (2000). Utility of perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), anti-saccharomyces cerevisiae (ASCA), and anti-pancreatic antibodies (APA) as serologic markers in

a population based cohort of patients with Crohn's disease (CD) and ulcerative colitis (UC). *Gastroenterology, 118*(4). doi:10.1016/S0016-5085(00)82501-9

Schoepfer, A. M., Trummler, M., Seeholzer, P., Seibold-Schmid, B., & Seibold, F. (2008). Discriminating IBD from IBS: comparison of the test performance of fecal markers, blood leukocytes, CRP, and IBD antibodies. *Inflamm Bowel Dis, 14*(1), 32-39. doi:10.1002/ibd.20275

Shirts, B., von Roon, A. C., & Tebo, A. E. (2012). The entire predictive value of the prometheus IBD sgi diagnostic product may be due to the three least expensive and most available components. In *Am J Gastroenterol* (Vol. 107, pp. 1760-1761). United States.

Silverberg, M. S., Satsangi, J., Ahmad, T., Arnott, I. D., Bernstein, C. N., Brant, S. R., . . . Warren, B. F. (2005). Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol, 19 Suppl A*, 5a-36a. Retrieved from http://dx.doi.org/

Snapper, S., & Abraham, C. (2020). Immune and microbial mechanisms in the pathogenesis of inflammatory bowel disease - UpToDate. In K. Robson (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/immune-and-microbial-mechanisms-in-the-pathogenesis-of-inflammatory-bowel-disease?sectionName=GENETIC%20SUSCEPTIBILITY&topicRef=4070&anchor=H8&source=see_link#H8

Strober, W., Fuss, I. J., & Blumberg, R. S. (2002). The immunology of mucosal models of inflammation. *Annu Rev Immunol, 20*, 495-549. doi:10.1146/annurev.immunol.20.100301.064816

Sura, S. P., Ahmed, A., Cheifetz, A. S., & Moss, A. C. (2014). Characteristics of inflammatory bowel disease serology in patients with indeterminate colitis. *J Clin Gastroenterol, 48*(4), 351-355. doi:10.1097/mcg.0000000000000083

Targan, S. R., Landers, C. J., Yang, H., Lodes, M. J., Cong, Y., Papadakis, K. A., . . . Hershberg, R. M. (2005). Antibodies to CBir1 flagellin define a unique response that is associated independently with complicated Crohn's disease. *Gastroenterology, 128*(7), 2020-2028. Retrieved from https://www.gastrojournal.org/article/S0016-5085(05)00569-X/fulltext?referrer=https%3A%2F%2Fwww.ncbi.nlm.nih.gov%2F

Turner, D., Ruemmele, F. M., Orlanski-Meyer, E., Griffiths, A. M., de Carpi, J. M., Bronsky, J., . . . Russell, R. K. (2018). Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care—An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr, 67*(2). Retrieved from https://journals.lww.com/jpgn/Fulltext/2018/08000/Management_of_Paediatric_Ulcerative_Colitis,_Part.24.aspx

Vasant, D. H., Paine, P. A., Black, C. J., Houghton, L. A., Everitt, H. A., Corsetti, M., . . . Ford, A. C. (2021). British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. *Gut, 70*(7), 1214-1240. doi:10.1136/gutjnl-2021-324598

Vijayvargiya, P., Busciglio, I., Burton, D., Donato, L., Lueke, A., & Camilleri, M. (2018). Bile Acid Deficiency in a Subgroup of Patients With Irritable Bowel Syndrome With Constipation Based on Biomarkers in Serum and Fecal Samples. *Clin Gastroenterol Hepatol, 16*(4), 522-527. doi:10.1016/j.cgh.2017.06.039

Walters, J. R. F., & Pattni, S. S. (2010). Managing bile acid diarrhoea. *Therap Adv Gastroenterol, 3*(6), 349-357. doi:10.1177/1756283x10377126

Wang, Z. Z., Shi, K., & Peng, J. (2017). Serologic testing of a panel of five antibodies in inflammatory bowel diseases: Diagnostic value and correlation with disease phenotype. In *Biomed Rep* (Vol. 6, pp. 401-410).

APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*